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(54) BENZODIAZONCINE METHOD

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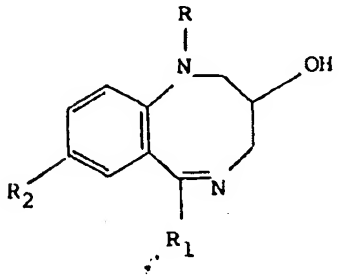
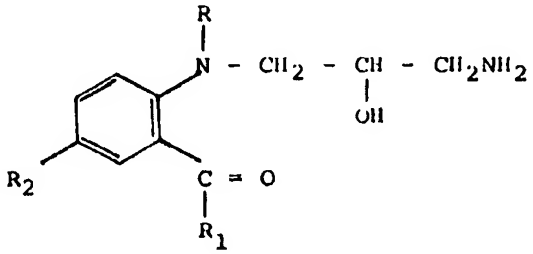
ABSTRACT OF THE DISCLOSURE

A method for producing 3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocines corresponding to the formula:

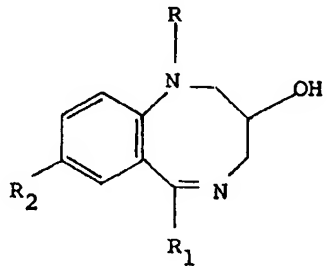


and pharmaceutically acceptable acid-addition salts thereof, wherein R represents a hydrogen atom or a methyl group, R_1 represents a phenyl group, a 2-halo-phenyl group or a 2-trifluoromethyl-phenyl group, and R_2 represents a hydrogen atom, a halogen atom, a nitro group or a trifluoromethyl group. In such method 2-aminobenzophenones corresponding to the formula:

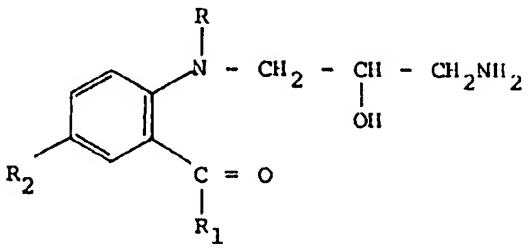


wherein R, R_1 and R_2 have the meanings given above, or addition salts thereof, are cyclized at an elevated temperature in the presence of an inert organic solvent.

The object of the present invention is to provide a method for producing 3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocines corresponding to the formula I:



and acid-addition salts thereof, wherein R represents a hydrogen atom or a methyl group, R_1 represents a phenyl group, a 2-halophenyl group or a 2-trifluoromethyl-phenyl group, and R_2 represents a hydrogen atom, a halogen atom, a nitro group or a trifluoromethyl group, characterized in that 2-aminobenzophenones corresponding to the formula II:



wherein R, R_1 and R_2 are as already defined, or the addition salts thereof, are cyclized at an elevated temperature in the presence of an inert organic solvent.

In this cyclization reaction, there may be used as inert organic solvents: low molecular weight monovalent or bivalent alcohols such as methanol, ethanol, propanol, isopropanol, butanols and ethylene glycol, acetic acid or

aprotic solvents such as benzene, toluene, xylene, dioxan, tetrahydrofuran, Sulfolane (thiocyclopentane 1-dioxide), or dimethyl sulfoxide. The cyclization reaction is preferably carried out at temperatures of between about 40°C and about 200°C. Generally speaking, most satisfactory yields are obtained at temperatures of between about 80°C and about 160°C, at normal or elevated pressure. If acetic acid is used as the solvent, however, the temperature should then be between about 40°C and about 100°C.

In many cases the cyclization may be improved by the addition of gaseous ammonia or an ammonium salt, such as ammonium chloride or ammonium sulfate.

The optimum cyclization conditions depend, inter alia, upon the nature of the substituents in the 2-aminobenzophenone. The ring is generally closed more readily and more completely if the nitrogen atom in the 1-position is methylated. In the case of 2-aminobenzophenones substituted in the 5-position, it may be particularly advantageous to use an acid addition salt thereof, the salts with hydrochloric acid, sulphuric acid or phosphoric acid being particularly suitable.

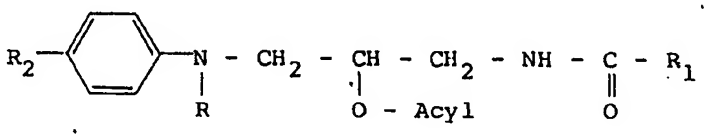
At the conclusion of the reaction, the reaction products may be processed in a conventional manner, and the products may isolated as bases, or in the form of salts with organic or inorganic acids, e.g. as hydrochlorides, sulphates, maleinates, etc.

In the above formulae, the optional halogen atom in the 2-phenyl group R_1, represents fluorine, chlorine or bromine; in the R_2 group it represents chlorine, bromine or iodine and preferably chlorine or bromine.

The 3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,

5-benzodiazocines of the above formula I are known as intermediate products useful in the manufacture of pharmacologically valuable 1,4-benzodiazepine derivatives. Furthermore, such 3-hydroxy-1,5-benzodiazocines have useful effects on the central nervous system. These compounds and their pharmaceutically applicable acid-addition salts, are useful anti-convulsives, muscle relaxants and sedatives, as may be determined by reference to published German Specification 23 53 165.

Published German Specification # 22 21 558 discloses a method for producing benzodiazocines of the preceding formula. In that method, acyldiamines corresponding to the formula:



wherein R, R_1 and R_2 are as hereinbefore defined and the acyl group is preferably an acetyl or benzoyl group, are cyclized using phosphorus oxychloride at temperatures of between 50°C and 105°C, and preferably between 110°C and 130°C, and the resulting 3-acyloxy-1,5-benzodiazocines are hydrolyzed, in a known manner, to the corresponding 3-hydroxy-1,5-benzodiazocines. The disadvantage of this known procedure is that the cyclization reaction ahd the subsequent hydrolysis proceed differently, depending upon the substituents on the phenyl rings of the acyldiamines. In many cases, the yields are also unsatisfactory.

It has already been proposed to produce 6-phenyl-1,5-benzodiazocine derivatives by cyclizing 2-(3-aminopropylamino)-benzophenone derivatives, but this method succeeds to only a limited extent. For example, in J. Org. Chem. 34 (1969), p, 179-183, M.E. DERIEG, RM. SCHWEININGER and R.I. FRYER describe

how, starting with 2-(β-benzyloxycarbonylalanyl-N-methyl-amido)-5-chlorobenzophenone, it is possible to obtain 8-chloro-3,4-dihydro-1-methyl-6-phenyl-1,5-benzodiazocine-2(1H)-one. However, any attempt to cyclize the non-methylated compound at the N_1-nitrogen atom leads, by dimerization, to a tetraaza-cyclohexadecane derivative.

2-(3-aminopropylamino)-5-chloro-benzophenone may, however, be cyclized somewhat more successfully to the desired 1,5-benzodiazocine. However, the initial compounds for this method are not easily available. They are obtained by hydrolyzing 9-chloro-1,2,3,5-tetrahydro-7-phenylpyrimido-[1,2-a],[1,4]-benzodiazepine. Another method produces the corresponding 2-(3-halopropylamino)-5-chlorobenzophenone. However, these products are not obtainable by directly alkylating 2-aminobenzophenones, but only by either hydrolyis of 7-chloro-1-(3-chloropropyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepine-2-one or from the reactive 2-tosylamido-5-chlorobenzophenone intermediate stage.

Statements made by M. STEINMANN and J.G. TOPLISS, in J.Pharm. Sci. (1969), p. 830-832, confirm the above-mentioned possibility of obtaining 1-methyl-1,5-benzodiazocine-2-one from 2-(β-benzyloxycarbonylalanyl-N-methylamido)-5-chlorobenzophenone. At the same time, however, the authors point out that, if use is made of a phthalimido group in order to introduce nitrogen into the 5-position, the desired 1,5-benzodiazocine derivative is not obtained, only ring-constricted quinolones being formed.

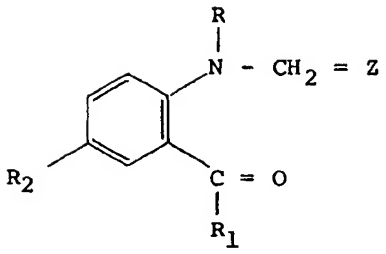
In contrast to this, the cyclization according to the present invention of the 2-(3-amino-2-hydroxypropylamino)-benzophenones of the above formula proceeds smoothly, with

good yields despite the presence of the β-located hydroxy group. This is surprising for several reasons. For instance, according to the relevant literature what was to be expected was a conversion to aminals, with the formation of a bicyclic 4, 1-oxepin-1,5-diazocine system. On the other hand, it would not have been impossible, during the reaction of the 2-(3-amino-2-hydroxy-propylamino)-benzophenone and, because the tendency to form a 7-ring system, for the 2-(2-hydroxypropylamino) group to react, without the participation of the terminal 3-amino group, to the 4,1-oxepin-semi-ketal stage, thus interfering considerably with formation of the desired 3-hydroxy-1,5-benzo-diazocine compounds.

As another advantage of this invention, it has been found that the aforementioned 2-(3-amino-2-hydroxypropylamino)-benzophenones can be produced, for example, both from the corresponding 2-(3-halo-2-hydroxypropylamino)-benzophenones of the general Formula III (see below) directly with ammonia and from well purified phthalimide compounds of the Formula IV (see below). In this case, it is not absolutely necessary to isolate the 2-(3-amino-2-hydroxypropylamino)-benzophenones at an intermediate stage. Instead, cyclization to a 3-hydroxy-1,5-benzodiazocine may be carried out in the reaction mixture itself. Another unpredictable advantage is that compounds of the general Formulae III and IV (see below) may be produced directly by reaction 2-amino-benzophenones of the general Formula V (see below) with epichlorohydrin or N-(2-3-epoxy-propyl)-phthalimide.

The 2-aminobenzophenones as used in the method of this invention may be produced by various known methods.

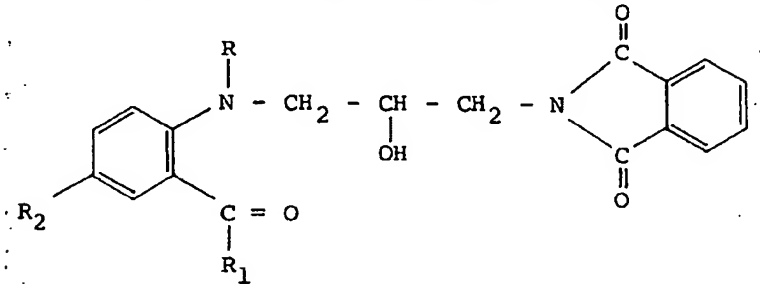
For example, compounds of the following formula III:



wherein R, R_1 and R_2 have the meanings hereinbefore given and Z represents a $CH-CH_2$ group or a $-CH(OH)-CH_2$-halogen group, the halogen atom preferably being chlorine or bromine, may be reacted with ammonia gas in the presence of an inert solvent. Suitable inert solvents are, for example, low molecular weight alkanols such as methanol, ethanol, propanol, isopropanol and butanols, and dioxan and tetrahydrofuran. Reaction temperatures of between 10°C and 60°C generally produce the desired compounds. The 2-aminobenzophenones so obtained may then be cyclized, as described above, at elevated temperature and, if necessary, at elevated pressure.

Such starting compounds need not be isolated from the reaction medium in which they are formed; instead, they may be converted directly into corresponding 1,5-benzodiazocines by heating in the reaction mixture.

According to another embodiment, the 2-aminobenzophenones of the general formula I may be obtained by acid or alkaline splitting of compounds of the following formula IV:



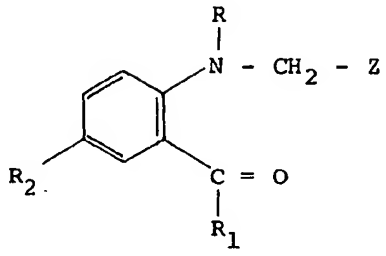
wherein R, R_1 and R_2 have the meanings already given above, by splitting off the phthaloyl group. In order to carry out acid fission, such compounds are preferably heated with concentrated aqueous hydrochloric acid. The 2-aminobenzophenones may be isloated from the reaction mixture as bases or as hydrochlorides, and may then be purified. It is advantageous to obtain the 2-aminobenzophenones in which R represents a methyl group as the hydrochlorides. The crude oils may also be used in the cyclization reaction.

In the case of alkaline fission of the phthaloyl group, compounds of the Formula IV are obtained by reacting with hydrazine, hydrazine hydrate, water-soluble low molecular weight primary amines such as methyl-, ethyl-, propyl- or butyl-amine, preferably methylamine or aminoethanol. The reaction is preferably carried out in the presence of low molecular weight alkanols such as methanol, ethanol, isopropanol, or mixtures thereof, possibly with the addition of water, and at the boiling point of the solvent. The compounds of the Formula II thus obtained, may be converted in the pure form, or in the form of crude oils as described above, by heating, preferably to 160°C, in the presence of a solvent, into the desired 1,5-benzodiazocines of the Formula I.

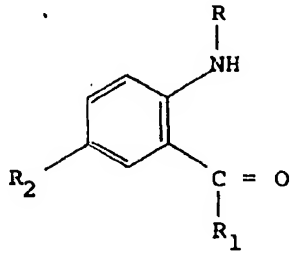
Compounds of the Formula II, obtained by hydrazinolysis or aminolysis, need not be isolated from their reaction medium, but may be converted directly into corresponding compounds of the Formula I by heating the reaction mixture. In many cases, the subsequent cyclization of compounds of the Formula II into the desired compounds of the Formula I proceeds at a reaction velocity such that, at the temperature at which the phthaloyl radical is split off, a partial to complete cyclization of the

2-aminobenzophenone takes place simultaneously.

Compounds of the Formula III:



wherein R, R_1 and R_2 and Z have the meanings already given, may also be obtained by known methods. Initial compounds of the Formula III, wherein Z signifies $-CH(OH)-CH_2$-halogen may be produced by reacting 2-aminobenzophenones of the Formula V:



wherein R, R_1 and R_2 have the meanings already given above, with epichlorohydrin or epibromohydrin, at temperatures below 100°C in the presence of acetic acid, for example.

Initial compounds of the Formula III, wherein Z represents a epoxyethyl group, may be obtained, according to the "HOUBEN-WEYL" methods described in Organische Chemie 6/3, p. 374 et seq. (1965), by reacting a 1,2-hydrin halide of the Formula III, in the presence of the strong base such as sodium or potassium hydroxide, and in an inert solvent such as ether, dioxan, tetrahydrofuran, benzene or toluene, with concentrated

aqueous alkali hydroxide solutions, at room temperature.

Phthalimide compounds of the Formula IV can be prepared from compounds of the Formula III, wherein Z may have two different meanings. Thus compounds of the Formula III, wherein Z is an epoxyethyl group may be reacted with phthalimide at an elevated temperature, in an inert solvent such as dimethylformamide. Using 1,2-hydrin halides of the Formula III makes it possible to produce corresponding phthalimides of Formula IV by reacting the former compounds with potassium phthalimide in the presence of an inert solvent such as dimethylformamide by a base-catalyzed reaction, in the presence of pyridine, for example, and at an elevated temperature. It is also possible to react 2-aminobenzophenones of the Formula V with N-(2,3-epoxypropyl)-phthalimide, at an elevated temperature, in the presence of acetic acid, to form phthalimide compounds of the Formula IV.

In producing compounds of the Formula I, wherein R represents a methyl group, it is possible to start with the corresponding 2-methylaminobenzophenones of the Formula V, wherein R_1 and R_2 have the meanings given above. It is also possible to introduce the methyl group into compounds of the Formula III, when 2 represents a $-CH_2-CH(OH)-CH_2$-halogen group or into compounds of the Formula IV, by methods known from the relevant literature, for example by reductive carbonyl-aminating with a formalin solution, in the presence of formic acid and at an elevated temperature (see the Leuckart-Wallach or Eschweiler-Clark reaction in H. KRAUCH, W. KUNZ, Reactions in Organic Chemistry (1976), p. 126 and 131), if R in these compounds represents a hydrogen atom.

The following Examples serve to illustrate the invention.

EXAMPLE 1

8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

232 g of 2-amino-5-chloro-benzophenone were heated to 60°C with 102 g of epichlorohydrin and 60 g of acetic acid. The product, which crystallized upon cooling, was placed in water, drawn off, and then extracted from 800 ml of acetone. With the crystalline product obtained from the concentrated mother liquid, the yield of 2-(3-chloro-2-hydroxypropylamino)-5-chloro-benzophenone was 279 g (86%). The melting point was between 105°C and 107°C.

16.2 g of the above 2-(3-chloro-2-hydroxypropylamino)-5-chloro-benzophenone were reacted in 50 ml of isopropanol and 50 ml of dioxan with 2.2 g of sodium hydroxide and 4.1 ml of water, for 10 hours, at room teperature. After the organic solvent had been drawn off in vacuo, the resulting crude oil was dissolved in chloroform. The chloroform phase was then washed until neutral with water, dried over sodium sulphate, and filtered. After the chloroform had been removed, an oil was obtained, recrystallizing this out of isopropanol/petroleum ether produced 8.0 g (55.6%) of 2-(2,3-epoxypropylamino)-5-chloro-benzophenone having a melting point of between 61°C and 62°C.

4 g of the above 2-(2,3-epoxypropylamino)-5-chloro-benzophenone were reacted in 400 ml of methanol with 12.0 g of ammonia gas, for 20 hours, at room temperature. After the solvent had been removed in vacuo, 3.6 g (85%) of 2-(3-amino-2-hydroxypropylamino)-5-chloro-benzophenone crystallised out of isopropanol/petroleum ether; the substance melted at between 125°C and 129°C.

3g of the above 2-(3-amino-2-hydroxypropylamino)-5-

chloro-benzophenone were heated in 100 ml of methanol with 0.6 g of ammonium chloride, for 20 hours, in a steel autoclave, at 140°C. The solvent was drawn off in vacuo, the substance was isolated out of chloroform, and aluminum oxide of activity stage II was removed by chromatography with chloroform/methanol. 2.0 g (70.9%) of 8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1, 5-benzodiazocine were obtained in the form of an oil. The hydrochloride, crystallized out of isopropanol/ether, melted at between 206°C and 208°C.

EXAMPLE 2

8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1, 5-benzodiazocine.

16.2 g of 2-(3-chloro-2-hydroxypropylamino)-5-chloro-benzophenone were heated in 19 ml of formic acid and 9.5 ml of a 37% formalin solution, for 2.5 hours in a water-bath. The solution was then poured onto ice and neutralized with a dilute aqueous solution of sodium hydroxide. The reaction product was reduced in chloroform, the solution washed with a sodium carbonate solution, dried, and the chloroform drawn off. This produced 19.2 g of crude oil containing 78% of 2-(3-chloro-2-hydroxypropyl-methylamino)-5-chloro-benzophenone, corresponding to a yield of 88.6%. The substance, crystallized out of isopropanol/petroleum ether, melted at between 71°C and 72°C. The crude oil could be used without purification.

18.6 g of this crude oil were reacted in 30 ml of isopropanol, with 2.4 g of sodium hydroxide, in 4.5 ml of water for 12 hours, at room temperature. The filtered solution was drawn off in vacuo, the crude oil taken up in chloroform and processed. 15 g of 2-(2,3 epoxypropyl-methylamino)-5-chloro-benzophenone were obtained in the form of an oil.

9 g of this 2-(2,3-epoxypropyl-methylamino)-5-chloro-benzophenone were reacted in a steel autoclave, for 10 hours at 150°C, with 5.1 g of ammonia gas, in 100 ml of ethanol. After drawing off the solvent in vacuo, 85.1% of a raw product containing 8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine were isolated, according to HPLC analysis. The compound, crystallized out of ether, had a melting point of between 169°C and 170°C.

EXAMPLE 3

8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

64.8 g of the 2-(3-chloro-2-hydroxypropylamino)-5-chloro-benzophenone, produced from 2-amino-5-chloro-benzophenone, dissolved in 200 ml of dimethylformamide, were dripped at 130°C, into a suspension consisting of 40.5 g of potassium phthalimide, 1.2 ml of pyridine, and 60 ml of dimethylformamide, in such a manner that the temperature was maintained at between 130°C and 140°C during the exothermal reaction. The solution was allowed to stand for a further 1.5 hours at the reaction temperature. After removal of the solvent in vacuo, the product was isolated from ether and the crude oil was crystallized out of isopropanol. This produced 64 g (73.6%) of 2-(3-phthalimido-2-hydroxy-propylamino)-5-chloro-benzophenone; the substance melted at between 131°C and 133°C.

22 g of the above 2-(3-phthalimido-2-hydroxypropylamino)-5-chloro-benzophenone were heated, for 1.5 hours under reflux, in 400 ml of methanol, with 5.5 g of hydrazine hydrate. The cooled solution was acidified with aqueous hydrochloric acid and filtered, and the filtrate was concentrated in vacuo. After being alkalinized, the base was isolated, using an aqueous sodium hydroxide solution, from chloroform. 11.0 g (71.4%) of 2-(3-amino-

2-hydroxy-propylamino)-5-chloro-benzophenone crystallized out of isopropanol.

For the cyclization, 3.0 g of 2-(3-amino-2-hydroxy-propylamino)-5-chloro-benzophenone were heated, in 80 ml of dioxan, with 1.7 g of ammonia gas in 50 ml of methanol, for 20 hours in an autoclave, at 140°C. After the reaction mixture has been processed, 1.9 g (67.3%) of 8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine were obtained. The melting point of the hydrochloride was between 206°C and 208°C.

EXAMPLE 4

8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

16.2 g of 2-(3-chloro-2-hydroxypropylamino)-5-chloro-benzophenone were heated in 19 ml of formic acid and 9.5 ml of a 37% formalin solution, for 2.5 hours, in a water bath. The solution was then poured onto ice and neutralized with a dilute aqueous sodium hydroxide solution. The reaction product was transferred into chloroform, the solution washed with a sodium carbonate solution, and the chloroform drawn off. This produced 19.2 g of crude oil containing 78% of 2-(3-chloro-2-hydroxypropyl-methylamino)-5-chloro-benzophenone, corresponding to a yield of 88.6%. The substance crystallized out of isopropanol/petroleum ether, melted at between 71°C and 72°C. The crude oil could be used without purification.

18.6 g of this crude oil were reacted, in 30 ml of isopropanol, with 2.4 g of sodium hydroxide in 4.5 ml of water, for 12 hours, at room temperature. The filtered solution was drawn off in vacuo, the crude oil taken up in chloroform and processed. This produced 15 g of 2-(2,3-epoxypropyl-methylamino)-5-chloro-benzophenone in the form of an oil.

15 g of the 2-(2,3-epoxypropyl-methylamino)-5-chloro-benzophenone, in the form of the crude oil, were reacted with 8.1 g of phthalimide and 0.5 ml of pyridine, dissolved in 100 ml of dimethylformamide, for 2 hours at between 130°C and 140°C. The substance isolated from chloroform, after removal of the solvent, was dissolved in isopropanol and the insolubles filtered out. This produced 15.0 g of 2-(3-phthalimideo-2-hydroxypropyl-methylamino)-5-chloro-benzophenone which melted at between 132°C and 134°C. A crystalline material, melting at between 128°C and 130°C,was obtained from toluene/petroleum ether. The two crystal systems were transferred into each other.

12.1 g of the 2-(3-phthalimido-2-hydroxypropyl-methylamino)-5-chloro-benzophenone were heated, in 75 ml of ethanol, with 1.5 g of hydrazine hydrate, for 1.5 hours under reflux. The solution was filtered hot and the filtrate concentrated in vacuo. The base was isolated in chloroform after treatment with an aqueous sodium hydroxide solution. 6.8 g (84.0%) of 8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine were obtained from ether. The base had a melting point of between 169°C and 170°C.

EXAMPLE 5

8-chloro-1-methyl-3-hydroxy-6-)2'-chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine.

31 g of 2-(3-chloro-2-hydroxypropylamino)-2,5-dichlorobenzophenone were heated with 38 ml of formic acid and 19 ml of a 37% formalin solution, for 3 hours under reflux. The solution was poured onto ice, neutralized with an aqueous sodium hydroxide solution, and extracted with chloroform. After the chloroform had been distilled off, 35.5 g of crude oil were obtained which contained, according to HPLC analysis, 55.5% of

2-(3-chloro-2-hydroxypropyl-methylamino)-2',5-dichlorobenzophenone.

18.6 g of this crude oil, dissolved in 100 ml of dimethylformamide were dripped, at 125°C, into a suspension of 10.2 g of potassium phthalimide in 1.5 ml of pyridine and 100 ml of dimethylformamide. This was allowed to stand for 2.5 hours at this temperature. After removal of the solvent, the crude product, isolated from chloroform, was recrystallized out of isopropanol. This produced 6.2 g of 2-(3-phthalimido-2-hydroxypropyl-methylamino)-2',5-dichlorobenzophenone having a melting point of between 186°C and 188°C.

6.0 g of this product were heated in 150 ml of ethanol with 0.7 g of hydrazine hydrate, for three hours, under reflux. The solvent was drawn off in vacuo from the hot-filtered solution. After the residue had been processed, 5 g of crude oil were obtained, which, according to HPLC analysis, produce 30% of cyclized product in addition to the 2-(3-amino-2-hydroxypropyl-methylamino)2',5-dichlorobenzophenone.

The crude oil was heated for a further 2 hours, to 150°C in an autoclave, in 100 ml of methane. This increased the proportion of cyclized product to 75%. This produced, after removal of the solvent, and removing aluminum oxide of activity stage II from the base by column chromatography, 2.8 g (67.2%) of 8-chloro-1-methyl-3-hydroxy-6-(2'-chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine. The base, recrystallized out of ether, had a melting point of between 176°C and 178°C. The hydrochloride, recrystallized from acetone, melted at 195°C.

EXAMPLE 6

8-chloro-1-methyl-3-hydroxy-6-(2'chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine.

29.0 g of 2-(3-chloro-2-hydroxypropylamino)-2',5-dichlorobenzophenone, dissolved in 75 ml of dimethylformamide, were dripped into a suspension of 16.4 g of potassium phthalimide in 1.3 ml of pyridine and 75 ml of dimethylformamide at 120 to 130°C and were left at this temperature for 2.5 hours. The crude oil, subsequently isolated out of chloroform, contained, according to HPLC analysis, 67.8%, in relation to the preliminary product, of 2-(3-phthalimido-2-hydroxypropylamino)-2',5-dichlorobenzophenone. The pure base had a melting point of between 143°C and 145°C.

39.9 g of the crude oil were heated under reflux, for 3 hours, with 32 ml of formic acid and 16 ml of a 37% aqueous formalin solution. After processing and recrystallizing out of isopropanol, 13.9 g of 2-(3-phthalimido2-hydroxypropyl-methylamino)-2',5-dichlorobenzophenone were obtained, with a melting point of between 186°C and 188°C.

7.5 g of the 2-(3-phthalimido-2-hydroxypropyl-methylamino)-2',5-dichlorobenzophenone were heated at 150°C, in an autoclave, with 150 ml of methanol and 0.9 g of hydrazine, for 2 hours. This produced, after processing, 3.3 g (63.5%) of 8-chloro-1-methyl-3-hydroxy-6-(2'-chloro-phenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine with a melting point of between 176°C and 178°C.

EXAMPLE 7

8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

19.6 g of 5-chloro-2-aminobenzophenone were heated with 20.0 g of N-(2,3-epoxypropyl)-phthalimide in 50 ml of acetic acid, for 14 hours, at about 90°C. The solution, diluted with chloroform, was poured onto ice and alkalinized with an aqueous sodium hydroxide solution. The product, isolated out of ether, was recrystallized with isopropanol. This produced 28.5 g (77.5%) of 2-(3-phthalimido-2-hydroxypropylamino)-5-chloro-benzophenone.

4.3 g of this 2-(3-phthalimido-2-hydroxypropylamino)-5-chloro-benzophenone were heated in an autoclave, with 0.5 g of methylamine in 150 ml of methanol, initially for 2 hours at 60°C and subsequently for 15 hours at 150°C. The crude oil obtained, after removal of the solvent in vacuo, had the aluminum oxide of activity stage II removed by cleaning. This produced 0.9 g (31.7%) of 8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine. The melting point of the hydrochloride was between 206°C and 208°C.

EXAMPLE 8

8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

24.5 g of 2-methylamino-5-chloro-benzophenone were heated with 10.2 g of epichlorohydrin and 6.0 g of acetic acid, for 72 hours at 70°C. After processing, 33.6 g of a crude oil containing 2-(3-chloro-2-hydroxypropyl-methylamino)-5-chloro-benzophenone were isolated. The product was used without further purification.

33.6 g of the crude oil, dissolved in 80 ml of dimethylformamide, were dripped at 130°C into a suspension

consisting of 20 g of potassium phthalimide, 1.5 ml of pyridine and 80 ml of dimethylformamide. After about 2 hours, the solvent was drawn off. The 2-(3-phthalimido-2-hydroxypropyl-methylamino)-5-chloro-benzophenone, isolated out of toluene, crystallized after addition of petroleum ether. The yield amounted to 22.3 g (49.7%) in relation to the 2-methylamino-5-chloro-benzophenone.

2.0 g of 2-(3-phthalimido-2-hydroxypropyl-methylamino)-5-chloro-benzophenone were heated in 50 ml of methanol with 6 ml of a 33% aqueous methylamine solution for 45 minutes under reflux. Processing consisted of drawing off the solvent in vacuo, dissolving the residue in chloroform, and washing with water. After drying and drawing off the solvent, the oleaginous residue was digested with ether. 1.2 g of 8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine (89.6%) were obtained in the form of a crude oil The product obtained by recrystallization had a melting point of between 169°C and 170°C.

EXAMPLE 9

8-chloro-1-methyl-3-hydroxy-6-(2'-chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine.

9.3 g of 2-amino-2',5-dichloro-benzophenone were heated with 7.8 g of N-(2,3-epoxypropyl)-phthalimide in 17.5 ml of acetic acid, for 17 hours at 90°C. The solution was poured onto ice and extracted with chloroform. After the chloroform had been distilled off, 15.5 g of 2-(3-phthalimido-2-hydroxypropyl-amino)-2',5-dichloro-benzophenone were obtained in the form of crude oil. This was heated with 14 ml of formic acid and 7 ml of a 37% aqueous formalin solution, for 3 hours under reflux. After the reaction product had been processed, the substance, isolated out of chloroform, was recrystallized out of isopropanol. This produced 5.5 g of 2-(3-phthalimido-2-hydroxypropyl-

methylamino)-2',5-dichloro-benzophenone having a melting point of between 186°C and 188°C.

2.0 g of 2-(3-phthalimido-2-hydroxypropylamino)-2', 5-dichloro-benzophenone were heated in 20 ml of aminoethanol, for 2.5 hours to 150°C. After the excess of aminoethanol had been drawn off in vacuo, the base was isolated out of chloroform. After purification by preparatory layer chromatography, 1 g (72.1%) of 8-chloro-1-methyl-3-hydroxy-6-(2'-chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine was obtained which, after recrystallizing out of ether, had a melting point of between 176°C and 178°C.

EXAMPLE 10

8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4,-tetrahydro-1, 5-benzodiazocine.

21.7 g of 2-(3-phthalimido-2-hydroxypropylamino)-5-chloro-benzophenone were reacted in 19 ml of formic acid and 9.5 ml of a 37% aqueous formalin solution, for 2.5 hours under reflux. After processing, 17.5 g (78.1%) of 2-(3-phthalimido-2-hydroxypropyl-methylamino)-5-chloro-benzophenone were obtained in crystalline form out of isopropanol/petroleum ether.

22.5 g of 2-(3-phthalimido-2-hydroxypropyl-methylamino)-5-chloro-benzophenone were heated with 100 ml of concentrated hydrochloric acid, for 7 hours under reflux. The cooled solution was filtered, the filtrate alkalinized with sodium hydroxide and extracted with chloroform. The 2-(3-amino-2-hydroxypropyl-methylamino)-5-chloro-benzophenone, contained in the crude oil after drying and drawing off the solvent, was dissolved in 100 ml of glacial acetic acid and heated for 1 hour at 90°C. The solvent was then drawn off and the substance was isolated out of chloroform. This produced 7.7 g (51.1%) of 8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1, 5-benzodiazocine having a melting point of between 169°C and 170°C.

The base was cyclized in a similar manner by heating

for 8 hours, under reflux, in isopropanol. According to HPLC analysis, the 1,5-benzodiazocine content amounted to 90%.

In the same way, the hydrochloride cyclized, under the conditions given above, in both acetic acid and isopropanol. The 1,5-benzodiazocine content, according to HPLC analysis, amounted to 80% and 70% respectively.

EXAMPLE 11

8-nitro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

8 g of 2-(3-bromo-2-hydroxypropyl-methylamino)-5-nitrobenzophenone were heated with a suspension consisting of 5.6 g of potassium phthalimide, 2.2 g of pyridine and 200 ml of dimethylformamide, for 3 hours at 130°C. The solution was then dispersed in water and the reaction product thus obtained was taken up in chloroform and isolated. Recrystallizing out of toluene produced 5.8 g (62.0%) of 2-(3-phthalimido-2-hydroxypropyl-methylamino)-5-nitrobenzophenone having a melting point of between 183°C and 188°C.

5.8 g of this phthaloyl compound were heated in 60 ml of concentrated hydrochloric acid, for 4 hours under reflux. The cooled colution was extracted with chloroform and the aqueous phase drawn off in vacuo until dry. After azeotropic distillation with toluene, in vacuo, the 2-(3-amino-2-hydroxy-propyl-methylamino)-5-nitrobenzophenone hydrochloride thus obtained was heated in 100 ml of acetic acid for 1 hour at 90°C. After distilling the solvent off in vacuo and alkalinizing with a dilute aqueous sodium hydroxide solution, 2.9 g (73.8%) of 8-nitro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine were isolated after extraction with chloroform. The substance, recrystallized out of methanol, had a melting

point of between 206°C and 209°C.

EXAMPLE 12

8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

6.4 g of 2-(3-chloro-2-hydroxypropylamino)-5-chloro-benzophenone in 150 ml of methanol were heated in an autocalve with 10.2 g of ammonia gas, for 18 hours at 60°C. After the solvent had been drawn off in vacuo, the substance was dissolved in chloroform. After treatment with a dilute aqueous sodium hydroxide solution, the chloroform was drawn off in vacuo. After recrystallizing the residue out of isopropanol, 4.4 g (73.1%) of 2-(3-amino-2-hydroxypropylamino)-5-chloro-benzophenone were obtained.

For the cyclization, 3 g of the 2-(3-amino-2-hydroxy-proplyamino)-5-chloro-benzophenone were heated in 90 ml of methanol, in an autoclave, for 18 hours at 90°C. After the reaction product had been processed, a 40% yield of 8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine was obtained. The melting point of the hydrochloride was between 206 and 208°C.

EXAMPLE 13

8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

16.1 g of 2-(3-chloro-2-hydroxypropylamino)-5-chloro-benzophenone, dissolved in 170 ml of methanol, were heated in a steel autoclave, with 8.5 g of ammonia gas, for 20 hours at 140°C. The solvent was then drawn off, the residue dissolved in chloroform, the solution washed with an aqueous sodium hydroxide solution and water,dried, and the solvent drawn off in vacuo. The 8-chloro-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine, purified chromatographically over aluminum oxide, was converted into the hydrochloride. 9.8 g (61.1%) of

of that compound were obtained, it had a melting point of between 206°C and 208°C.

EXAMPLE 14

8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

33.8 g of 2-(3-chloro-2-hydroxypropyl-methylamino)-5-chloro-benzophenone were heated, with 17.0 g of ammonia gas, in 300 ml of methanol, in a steel autoclave, for 12 hours at 150°C. After drawing off the solvent and alkalinizing with a dilute aqueous sodium hydroxide solution, the 8-chloro-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine was isolated out of chloroform. The yield of product, crystallized out of ether, was 21.5 g (71.5%). The melting point was 169-170°C.

EXAMPLE 15

8-chloro-3-hydroxy-6-(2'-chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine.

79.8 g of 2-amino-2', 5-dichloro-benzophenone were heated with 30.5 g of epichlorohydrin and 18.2 g of acetic acid, for 18 hours at 70°C. After dilution with chloroform, the solution was washed until neutral with water and the solvent then distilled off. 108 g of the crude product were obtained. According to HPLC analysis, this contained 75% of 2-(3-chloro-2-hydroxypropylamino)-2',5-dichloro-benzophenone. The benzophenone, crystallized out of isopropanol/petroleum ether, had a melting point of between 74°C and 76°C.

6.2 g of the crude oil containing the 2-(3-chloro-2-hydroxypropylamino)-2',5-dichloro-benzophenone were reacted, in 100 ml of methanol, with 3.4 g of ammonia gas, for 18 hours at 150°C in the autoclave. The reaction mixture was processed

and purified by column chromatography. The 8-chloro-3-hydroxy-6-(2'-chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine, occurring in the form of an oil, was converted into the hydrochloride in an ether solution with hydrogen chloride. The product, crystallized out of acetone, had a melting point of between 174°C and 178°C.

EXAMPLE 16

8-chloro-1-methyl-3-hydroxy-6-(2'-chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine.

6.3 g of 2-(3-chloro-2-hydroxypropyl-methylamino)-2',5-dichloro-benzophenone were dissolved in 50 ml of ethanol and heated with 4.4 g of ammonia gas, in 80 ml of ethanol, for 20 hours in an autoclave at 150°C. The crude base obtained after processing the reaction mixture was purified chromatographically. Recrystallizing out of ether produced 1.2 g (56.5%) of 8-chloro-1-methyl-3-hydroxy-6-(2'-chlorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine having a melting point of between 176°C and 178°C.

EXAMPLE 17

8-bromo-1-methyl-3-hydroxy-6-(2'-fluorophenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine.

34.7 g of 2-amino-5-bromo-2'-fluorobenzophenone were heated with 12.0 g of epichlorohydrin and 7.1 g of acetic acid, for 5 hours at 60°C. The 2-(3-chloro-2-hydroxypropylamino)-5-bromo-2'-fluorobenzophenone crystallized out of isopropanol/petroleum ether with a melting point of between 119°C and 121°C. The yield was 27.2 g (59.6%).

18.2 g of 2-(3-chloro-2-hydroxypropylamino)-5-bromo-2'-fluorobenzophenone were reacted with 18 ml of formic acid and 9 ml of a 37% aqueous formalin solution, for 3 hours at reflux temperature, and were then processed. This produced a

crude oil containing, according to HPLC analysis, 75% of 2-(3-chloro-2-hydroxypropyl-methylamino)-5-bromo-2'-fluoro-benzophenone.

9.6 g of this crude oil were then reacted in 130 ml of ethanol with 3.4 g of ammonia, for 20 hours at 80°C and then processed. After the aluminum oxide of activity stage II had been removed by column chromatography with chloroform/ethanol, and after recrystallizing with ether, 3.2 g (49%) of 8-bromo-1-methyl-3-hydroxy-6-(2'-fluoro-phenyl)-1,2,3,4-tetrahydro-1,5-benzodiazocine were obtained, with a melting point of 223°C.

EXAMPLE 18

3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

17.8 g of 2-aminobenzophenone were reacted with 9.2 g of epichlorohydrin and 5.4 ml of glacial acetic acid, for 18 hours at 60°C. 27.3 g of the crude product, isolated after processing, contained, according to HPLC analysis, 75% of 2-(3-chloro-2-hydroxypropylamino)-benzophenone. The product, which crystallized out of ether, melted at between 73°C and 75°C.

11.7 g of the crude product were reacted in 100 ml of methanol with 8.0 g of ammonia gas, for 16 hours at 150°C, in an autoclave. After the solvent had been drawn off, the reaction product was distributed between toluene and dilute aqueous hydrochloric acid. After alkalinizing with an aqueous sodium hydroxide solution, 3.1 g (40.2%) of 3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine were extracted with methylene chloride. The substance, crystallized out of ether, melted at between 149°C and 151°C.

EXAMPLE 19

1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

10.6 g of 2-methylaminobenzophenone were reacted with

5.2 g of epichlorohydrin and 3.0 g of glacial acetic acid, for 24 hours at 60°C. 14.4 g of isolated 94% (according to HPLC analysis) 2-(3-chloro-2-hydroxypropyl-methylamino)-benzophenone were reacted, without further purification, with 10.0 g of ammonia gas in 300 ml of methanol, for 12 hours at 150°C in an autoclave. After processing, 7.2 g of 1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine were isolated. The salt of maleic acid crystallized out of isopropanol and had a melting point of between 135°C and 137°C.

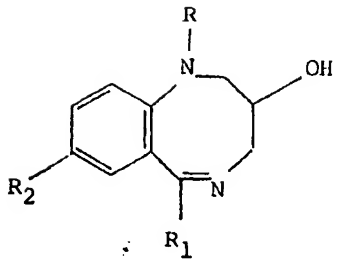
EXAMPLE 20

8-trifluoromethyl-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine.

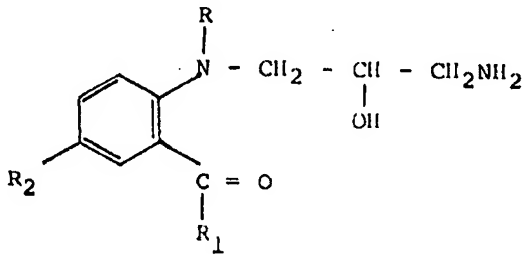
6.0 g of 2-(3-phthalimido-2-hydroxypropyl-methylamino)-5-trifluoro-methyl-benzophenone were heated in 60 ml of concentrated hydrochloric acid, for 4 hours under reflux. The cooled solution was extracted with chloroform, and the aqueous phase drawn off in vacuo until dry. After azeotropic distillation with toluene in vacuo, the 2-(3-amino-2-hydroxypropyl-methylamino)-5-trifluoromethyl-benzophenone hydrochloride thus obtained was heated in 100 ml of acetic acid, for 1 hour, at 90°C. After the solvent had been distilled off in vacuo, and after alkalinizing with a dilute aqueous sodium hydroxide solution, an oily material containing 8-trifluoromethyl-1-methyl-3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocine was isolated.

Having described what is believed to be the best mode by which the invention may be performed, it will be seen that the invention may be particularly defined as follows:

A method for producing 3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocines corresponding to the formula:



and pharmaceutically acceptable acid-addition salts thereof, wherein R represents a hydrogen atom or a methyl group, R_1 represents a phenyl group, a 2-halo-phenyl group or a 2-trifluoromethyl-phenyl group, and R_2 represents a hydrogen atom, a halogen atom, a nitro group or a trifluoromethyl group, characterized in that 2-aminobenzophenones corresponding to the formula:

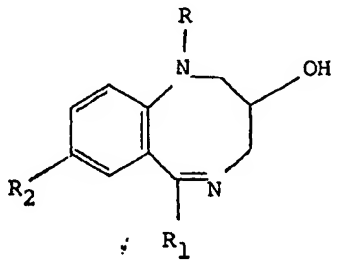


wherein R, R_1 and R_2 have the meanings given above, or addition salts thereof, are cyclized at an elevated temperature in the presence of an inert organic solvent.

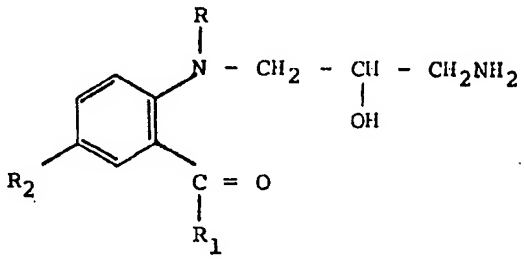
The foregoing is a description of a preferred embodiment of the invention which is given here by way of example only. The invention is not to be taken as limited to any of the specific features as described, but comprehends all such variations thereof as come within the scope of the appended claims.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for producing 3-hydroxy-6-phenyl-1,2,3,4-tetrahydro-1,5-benzodiazocines corresponding to the formula:



and pharmaceutically acceptable acid-addition salts thereof, wherein R represents a hydrogen atom or a methyl group, R_1 represents a phenyl group, a 2-halo-phenyl group or a 2-trifluoromethyl-phenyl group, and R_2 represents a hydrogen atom, a halogen atom, a nitro group or a trifluoromethyl group, characterized in that 2-aminobenzophenones corresponding to the formula:



wherein R, R_1 and R_2 have the meanings given above, or addition salts thereof, are cyclized at an elevated temperature in the presence of an inert organic solvent.

2. A method as claimed in Claim 1 and in which the cyclization is effected at a temperature of from about 40°C to about 200°

3. A method as claimed in Claim 2 and in which the cyclization is effected at normal or elevated pressure.

4. A method as claimed in Claim 3 and in which the cyclization is effected at a temperature of from about 80°C to about 160°C.

5. A method as claimed in Claim 2, in which the cyclization is effected at a temperature of from about 40°C to about 100°C and in which the inert organic solvent is acetic acid.

6. A method as claimed in Claim 4 and in which said inert organic solvent is a low molecular weight monovalent or bivalent alkanol.

7. A method as claimed in Claim 6 and in which said inert organic solvent is selected from the group consisting of methanol, ethanol, propanol, isopropanol, butanols and ethylene glycol.

8. A method as claimed in Claim 4 and in which said inert organic solvent is an aprotic solvent.

9. A method as claimed in Claim 8 and in which said aprotic solvent is selected from the group consisting of benzene, toluene, xylene, dioxan , tetrahydrofuran, thiocyclopentane 1-dioxide and dimethyl sulfoxide.

10. A method as claimed in Claim 1 and in which the cyclization of the 2-aminobenzophenone is effected in the reaction mixture in which such 2-aminobenzophenone is produced.

11. A method as claimed in Claim 1 and in which the cyclization is carried out in the presence of gaseous ammonia or an ammonium salt.

12. A method as claimed in Claim 11 and in which said ammonium salt is ammonium chloride or ammonium sulfate.